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Subject: Consult Review for BLA 98-0261 (REBIF (interferon βla) Pre-filled Syringes)
INC98.044

To: Stephanie Simek, Regulatory Coordinator, Cytokine and Gene Therapy Branch DARP, OTRR HFM-591;
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Through: Patricia Cricenti, Branch Chief, CDRH/ODE/DDIGD/GHDB, (HFZ-480)_____

Through: Eugene Berk, CDRH/ODE/POS, (HFZ-404)_____

I. Introduction

Serono has submitted a new application for REBIF (interferon β 1a). The product is formulated in a pre-filled 1-ml glass syringe with a XXXXXXXXXX plunger rod and rubber stopper. The syringe is half-filled to 0.5 ml for both REBIF 22 and 44 mcg formulations.

II. Device Description

The primary container used for REBIF solution for injection is a glass syringe with a stainless steel needle. The syringe components include a 1-ml XXXXXXXXXX glass barrel with an integral needle cannula (XXXXXXXXXX stainless steel), a stopper made of a synthetic rubber, and a XXXXXXXXXX plunger rod. The syringe has a nominal capacity of 1 ml with a needle gauge of 27G X ½ inch in length. The needle is affixed to the barrel tip with medical usage adhesive.

III. Review of Device Master Files

The information provided below in this consultation has been done based directly on review of the Master Files. Therefore, **the information is considered confidential.** FDA was authorized by XXXXXXXXXX on behalf of Serono Laboratories to access Drug Master File XXXXXXXXXX (identical to Device Master File XXXXXXXXXX) in a letter dated August 22, 1997. A letter of authorization dated August 29, 1997, by XXXXXXXXXX is provided for Master File XXXXXXXXXX.

The XXXXXXXXXX Syringe System is provided by XXXXXXXXXX. The components are manufactured, packaged and sterilized by XXXXXXXXXX. The syringe components are assembled by the pharmaceutical companies. The placement of the stoppers is done by pharmaceutical customers after syringe filling. The stoppers and needle shields are provided to XXXXXXXXXX by the XXXXXXXXXX.

A. The device component review:

1. The barrel is made from USP XXXXXXXXXX glass with an affixed needle and serves as a reservoir for containing the pharmaceutical. The barrels can be assembled with the customer's choice of needle gauge and length. The barrel sizes available are 0.5 to 20 ml. XXXXXXXXXX. With this application a 1-ml syringe with a 27G ½" needle has been chosen.

Comments: The glass material used in the manufacturing meets the U.S.P. requirements. This material was used in preamendment devices and continues to be used in drug/device combinations up to the current date. It is considered safe for this intended use.

The syringe should have barrel markings as defined in ISO 7886-1. It is recognized that the intent of the product is for single use (one dose). However, there may be a need to give a partial dose or for some reason, only a partial dose is given. The user would be unable to determine that partial dose without the gradations on the barrel. According to the Master File from XXXXXXXXXX. On Page 393 and Page 396 of the information received for consultation, there is some implication that this is true but it should be verified if important as explained above for this product. The decision to require this rests with CBER. For marketing clearance for a standard piston syringe, this is required by CDRH for volumetric/dose accuracy.

2. The plunger rod is made of XXXXXXXXXX. The rods may be provided in customer specified colors. The threaded plunger rod fits into the stopper.

   Comments: This does not raise new questions of safety because there is no contact with the material of the plunger in the fluid pathway. The materials are the types generally used in piston syringes. The plunger rods are non-sterile.

3. The plunger stopper is made of XXXXXXXXXX. The plunger stopper seals the flange end of the barrel and functions as a piston to deliver the drug.

   Comments: Please see number 5 below.

4. The needle cannula is made from XXXXXXXXXX stainless steel and is affixed to the barrel by an epoxy adhesive. The needle is XXXXXXXXXX to ease needle penetration. The needle is covered by a rubber needle shield used to protect the needle tip and seal the cannula opening during drug storage. The needle meets ISO #7864.

   Comments: The stainless steel is a common material used for hypodermic needles and does not raise new questions of safety.

5. Elastomeric Closures - Plunger stoppers and needle shields are the elastomeric components intended for use with XXXXXXXXXX barrels. They seal both ends of the filled syringe. They may be formulated of synthetic or natural rubber compounds.

   Rubber formulations that are offered in the XXXXXXXXXX system are subjected to initial qualification testing. The testing that they must pass according to USP <381> includes cytotoxicity, acute systemic toxicity and intracutaneous reactivity, physicochemical tests, and hemolysis. The coating used for the stoppers meet the USP Section <88> for Intracutaneous and Systemic Toxicity studies. The elastomeric closures are observed for any defects and have had functional testing for leakage of drug around the stopper. The materials have been tested and passed USP requirements for extractables.

   Comments: CDRH follows the ISO 10993-1 for the biological evaluation of piston syringes. Using this standard, the device category for this specific device is external communicating device, blood path, indirect and a contact duration of greater than 30 days. The testing required to be done and passed is Cytotoxicity, Sensitization, Systemic toxicity (acute), Sub-chronic toxicity (sub-acute toxicity), Genotoxicity, Haemocompatibility, Chronic Toxicity, and Carcinogenicity.

   The butyl rubber stopper and barrier coating XXXXXXXXXX is located in the fluid pathway and is more of a concern than the needle seal. Any additional testing would be needed more for this component.

The sponsor may have some justification for not doing all of the testing I have listed in the previous paragraph. For example, are the materials identical to materials used in a similar device for the same intended use? As you will note, the USP requirements are less than the ones outlined by the ISO standard. CBER may have reason to have different requirements from CDRH especially if you accept USP criteria.

Please note on Page 422 of the NAmSA report for the XXXXXXXXXX, the Cytotoxicity test conclusion is XXXXXXXXXX. The manufacturer should offer some explanation for this result. Did they do further testing to justify the acceptance of this result? XXXXXXXXXX.

I am unable to determine from the Master File or the submission from Serono if the stopper or the inert covering for the rubber stopper is compatible with the biological product (REBIF). According to the manufacturer of the syringe components, the exact formula of the plunger stopper is specified by the customer. The compatibility of the rubber stopper with the product is the customer's responsibility. Serono should provide that information so that the components will be safe for a container closure system for this specific product. Compatibility and stability data of biologics and drugs for prefilled devices are not within the domain of CDRH review.

B. Sterilization Review

Sterilization Information for Barrels with Needles	
Sterilization Method	XXXXXXXXXX
Validation Method	XXXXXXXXXX
SAL	XXXXXXXXXX
Packaging	XXXXXXXXXX
ETO Residues	XXXXXXXXXX
Pyrogen Test Method	XXXXXXXXXX

Sterilization Information for XXXXXXXXXX Rubber Component	
Sterilization Method	XXXXXXXXXX
Validation Method	XXXXXXXXXX
Packaging	XXXXXXXXXX
SAL	XXXXXXXXXX
Dose	XXXXXXXXXX
Pyrogen Test Method	XXXXXXXXXX

Comments: The sterilization information provided in the Master File is summarized in the above tables. This information meets all of the criteria required for terminal device sterilization. This review for sterility does not include the Aseptic Fill Process. For pre-filled devices using Aseptic Processing, CDRH currently resorts to consultative review with CDER.

C. Labeling

A request for review of the product labeling was not included in this consult. In the following list is some information that would be required by CDRH in the labeling for a syringe and needle.

1. The prescription statement should appear somewhere on the labeling.
2. "Single Use" statement is required for all non-reusable devices. The device label should include the size of the syringe and the needle gauge and length.

3. Instructions for use of this specific product (may be included on package insert).

For more information on labeling you may wish to refer to the guidance document entitled *GUIDANCE ON THE CONTENT OF PREMARKET NOTIFICATION [510(K)] SUBMISSIONS FOR PISTON SYRINGES.* This document may be found under Syringes on the Internet at http://www.fda.gov/cdrh/indexps.html#s.

IV. Conclusion

This consult covers the characteristics of the device components that would be considered in a premarket review. The devices have been available to pharmaceutical companies for NDA/ANDA for particular drug filling for a number of years. Changes have occurred over time that have been updated in the Master File. This review is based on the May 30, 1997 amendment to the XXXXXXXXXX file.

Comments are included for your use and points of concern have been identified. I am available to help if you have any questions about this consultation.

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